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Multi-trait Polygenic Prediction of Nicotine and Alcohol Dependence

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Abstract:

Alcohol and Nicotine Dependence (AD/ND) are enduring clinical problems resulting from chronic exposure. While their SNP-heritability ranges from 13-50%, leveraging polygenic scores (PS) to predict AD/ND has been limited. We examined a set of multi-trait polygenic models of AD and ND using known pre- and co-morbid phenotypes. Polygenic scores were constructed for eight traits that fell into the following categories: Personality traits, Externalizing and Internalizing behaviors, and neurocognitive, as well as other related phenotypes); height served as a control. Linkage Disequilibrium-adjusted BLUP-PS were derived in a non-overlapping sample of 6344 individuals of European ancestry (prevalence AD=35%; ND=46%) using approximately 1.8M loci. Multiple regression analyses examined the independent and joint effects of BLUP-PS before/after accounting for age, sex, and ancestry. Zero-order correlations between PS ranged from -0.001 (Depression:AUDIT-C) to 0.365 (Depression:Neuroticism) and followed expected directional effects. The amount of variance explained for individual BLUP-PS ranged from 0.1% [alcohol consumption] to 3.2% [educational attainment] for ND, and 0.1%[risk taking] to 0.2%[alcohol consumption] for AD. On the contrary, their joint effects accounted for a significant amount of variance over and above covariate effects for ND (R^2= 6%[SE=0.9%]), but not AD (R^2= 0.4%[SE=0.2%]). Analyses were also replicated using the traditional p-value threshold approach, which accounted for less phenotypic variance and biased estimates of pleiotropy. Overall, BLUP-PS effects are modestly confounded, but have differential, albeit enhanced predictive utility when jointly modeled to predict ND and AD. BLUP-based measures should be preferred over the traditional PS approaches in order to maximize the translation of GWAS signals.